Prostate-Specific Antigen Screening for Prostate Cancer in Older Men in the United States of America

Amanda Black\textsuperscript{a} Christine D. Berg\textsuperscript{b}

\textsuperscript{a}Division of Cancer Epidemiology and Genetics, and \textsuperscript{b}Division of Cancer Prevention, National Cancer Institute, Rockville, Md., USA

Abstract
Prostate cancer, like many diseases, is more common in older men. Although an estimated 1 in 7 men will be diagnosed with it, the majority of these men will not die from prostate cancer. The latent nature of this disease, the use of screening with prostate-specific antigen (PSA) testing and the greater risk of dying from causes other than prostate cancer contribute to this disparity. As the US population continues to age, prostate cancer screening and disease management presents an increasingly important public health issue. We discuss the current PSA screening recommendations and practices in the USA and the benefits and harms of screening older populations.

Introduction
Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer mortality in men in the USA [1]. The overall lifetime risk of being diagnosed with prostate cancer has doubled since the introduction of prostate-specific antigen (PSA) screening from approximately 8% in the 1980s to 16% in 2009. Considerable evidence from autopsy and cohort studies has consistently illustrated the latent nature and long natural history of prostate cancer [2]. Traditionally, men with prostate cancer presented with clinical symptoms (indicative of advanced disease) and at older ages. As a result of the widespread use of PSA testing, nowadays men are more often diagnosed with asymptomatic disease (clinically localized disease) and at younger ages. However, more than 60% of all prostate cancers are still diagnosed in men aged 65 years or older [3]. Clinically localized disease represents about 82% of the cancers in this age group and carries a 5-year relative survival of nearly 100%. While the average life expectancy of US males aged 75 years is about 10 years, the presence or absence of comorbid conditions can have a dramatic effect on an individual’s life expectancy [4]. For example, a healthy man aged 75 years may live an additional 14 years or more, whereas a man aged 65 years with severe lung disease may survive only a few more years. As men with a life expectancy of less than 10 years have no or limited potential to benefit from PSA screening, no professional organization currently recommends screening men who are expected to live for less than 10 years.
Prostate cancer is recognized as having a long latent history; thus, it is plausible that many older men would not have been diagnosed with cancer in the absence of screening. Further, the life expectancy of older men is reported to be almost identical in those not undergoing treatment for their localized cancer to those undergoing definitive treatment, suggesting perhaps that active efforts to identify all prostate cancers in older men should not be pursued [5]. In the next 20 years, the number of men aged 65 years and over is projected to almost double, increasing from 17 million to 32 million, exacerbating the need for effective prevention and disease control interventions in older men to reduce unnecessary cancer diagnoses and resultant treatment [6]. We discuss the use of PSA screening as a tool to detect prostate cancer in men aged 65 years and older.

Screening Recommendations for Older Men

In 1986, the Food and Drug Administration approved the PSA test as a way to monitor PSA levels in men following treatment to determine whether prostate cancer had been successfully treated. In 1994, PSA testing approval was expanded, not as a routine screening test, but as an aid in the detection of prostate cancer in men older than 50 years in combination with digital rectal exam.

No professional organization currently recommends screening older men for prostate cancer. The American Cancer Society, American Urological Association and National Comprehensive Cancer Network all recommend annual PSA screening for men aged 50 years and older if they have more than a 10-year life expectancy [7–9]. The US Preventive Services Task Force does not recommend screening for prostate cancer in men aged over 75 years regardless of life expectancy (the median life expectancy of men in the USA aged 75 years is about 10 years) [10]. The American Geriatric Society recommends that screening should be individualized rather than setting age-specific guidelines. All organizations recommend discussion between physician and patient of the risks and benefits of screening.

Ideally, screening guidelines should be based on level I evidence from high-quality randomized controlled trials. Two large randomized controlled trials of prostate cancer screening recently reported their findings; unfortunately, men aged 75 or over were excluded from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, and men aged 65–74 years have not as yet been demarcated in either trial [11, 12]. As such, there is a distinct lack of evidence to support screening older men; instead, the current guidelines are based on evidence from autopsy and cohort studies that provide relatively consistent evidence that PSA screening confers no benefit and may actually result in harm in older men.

Benefits of a PSA Test

The findings from the ERSPC of a mortality reduction of 20% in men in the screened arm compared to the control arm suggest that there may be a benefit of PSA testing [11]. However, the analysis was restricted to the core age group of those aged 55–69 years. PLCO analyses included men aged 55–74 years at entry and demonstrated no reduction in prostate cancer-specific mortality in men randomized to the intervention arm compared to the control arm [12]. The null finding in the PLCO may be attributable, in part, to the widespread use of PSA testing in the control arm; an estimated 46% of men randomized to the nonscreening arm underwent PSA screening [13]. Contamination in the control arm of the ERSPC is presumed to be lower, ranging from 7 to 35% in the countries that assessed contamination [13]. As neither the PLCO nor the ERSPC recruited men aged 75 years or over, the benefits of screening in this older age group remain unknown. The ERSPC and PLCO teams have discussed a joint analysis of the two trials and it is likely that future post hoc analyses will include examination of subgroups including men aged 65–74 years to investigate the potential benefit of PSA screening in reducing mortality from prostate cancer in these older men.

Harms of a PSA Test

A PSA test is a simple, inexpensive, noninvasive method to detect prostate cancer. Patients are generally accustomed to providing blood samples when they visit their physician, and a blood draw has negligible side effects. It is the multiple downstream consequences associated with the practice of PSA screening, however, that may be detrimental to the patient. If a PSA test is considered to be abnormal, the next step is often a transrectal prostate needle biopsy. As with most surgical procedures, anxiety, inconvenience and discomfort are anticipated, but prostate biopsies are accompanied by additional common side effects including blood in the urine, stool and semen, and
pain while urinating. More serious complications such as urinary tract infections, urinary retention, incontinence, erectile dysfunction, bleeding, cardiovascular events and sepsis are less common but do occur [14]. Curative treatment of advanced-stage cancer is not currently feasible. Treatment is an option for prostate cancer diagnosed at an early stage, and radical prostatectomy is the most common and most aggressive treatment option [15]. The complications of prostatectomy are similar to those observed with biopsy, and the most serious side effect is mortality due to the treatment [16]. More importantly, studies have shown that older men are more likely to experience surgical complications [17]. Both radiation therapy, administered as either external beam or brachytherapy, and hormone therapy (usually androgen deprivation) are also accompanied by unwanted side effects in many patients. Radiation therapy may lead to urinary, gastrointestinal and sexual complications, whereas the consequences of hormone therapy include bone density loss, hot flushes, adverse body composition, cardiovascular disease and diabetes [14].

These complications may be acceptable to men if the benefits of diagnosis and treatment outweigh the harms. However, both the ERSPC and PLCO trials demonstrated substantial overdiagnosis in the intervention arms, and further, the ERSPC reported that 48 men would have to be treated to prevent 1 death from prostate cancer in the time frame reported [11]. It is of note that this number may be an overestimate; Draisma et al. [18] recently demonstrated how the population context and the definitions used for lead time and overdiagnosis may influence study results. Nevertheless, not only are many men needlessly diagnosed with a cancer that may never have become apparent in their lifetime had they not been screened, but they are also subjected to unnecessary treatment and the accompanying risks of surgery.

**PSA Screening Practices in Older Men**

Unlike PSA screening, colorectal cancer screening is recommended by all major professional medical societies and guideline-issuing organizations; yet, older men are more likely to undergo screening for prostate cancer than for colorectal cancer [19]. PSA screening rates increase steadily from the age of 50 years, peaking in men aged 70–79. Data from the 2005 National Health Interview Survey showed that 52% of men aged 75 or over had had a PSA screening test in the past 2 years and, more worryingly, that 42% of men predicted to live less than 5 years reported having had recent prostate cancer screening [20]. Similarly, survey data from a study conducted by the Centers for Disease Control and Prevention reported that during a 2-year period, 72% of men aged 80 or older underwent PSA screening, and data from the 2006 Behavioral Risk Factor Surveillance System showed that about 60% of men aged over 75 years reported having had a PSA test in the past year [21]. In addition to self-reported PSA test use from these surveys, an analysis of linked data from the US Department of Veterans Affairs and Medicare claims data found that more than half of men aged 70 years or older and more than one third of men aged 85 years or older were screened in 2003 [22]. Perhaps the greatest concern resulting from these findings is the apparent lack of delineation between which men may benefit from PSA testing and those who have no potential for benefit; the latter study showed no difference in the rate of PSA testing in men aged 85 years or older in best health (34%) compared with those in worst health (36%). The most recent estimate of PSA testing, derived from medical chart audits of community-based family medicine practices, suggests that about three quarters of men aged 75 years or older had undergone a PSA test in the past year [23]. Despite the varying estimates of PSA use between studies, it is clear that PSA testing is being overutilized, and many older men are being inappropriately screened for a disease which will not kill them.

Although all screening guidelines also recommend that the patient be counseled on the pros and cons of undergoing a PSA test, there is little evidence to suggest that this advice is followed. A review of the medical charts of a sample of older Veterans Affairs patients reported that almost none of the PSA tests performed were requested by the patient [24]. Similarly, a study of the 2000 National Health Interview Survey found that 88% of older men who were screened for prostate cancer reported that their doctor first suggested screening, and only two thirds reported having a discussion with their doctor about the advantages and disadvantages of PSA screening [25]. Fear of litigation may be a contributor to the absence of discussion and considerable rates of PSA screening. For example, in 2001 a patient sued his physician because he did not receive a PSA test and was subsequently diagnosed with prostate cancer [26]. His physician lost the case and paid USD 1 million because experts stated that they always perform a PSA test without discussion. In this instance, and unfortunately as is so often the case, performing a PSA test without discussion was considered standard of care. Although this is commonly the default option, the available empirical evidence cannot support...
it as ‘best practice’. Financial incentives may also play a role in PSA screening. Medicare began coverage of PSA screening in 2000, paying for one PSA test per year if the patient shows no signs or symptoms of prostate cancer, undoubtedly contributing to the high level of PSA testing in older men. Indeed, a recent study showed higher levels of PSA testing in Veterans Affairs hospitals with primary care incentives compared to institutions without incentives [27].

**Risk of Dying from Prostate Cancer**

At birth, males carry a lifetime risk of dying from prostate cancer of less than 3% [28]. If they live to 60, 70 or 80 years of age, this risk increases marginally to less than 4%. So, despite the high incidence of prostate cancer, older men are more likely to die from other causes, such as cardiovascular disease [29]. Studies of Swedish men with localized prostate cancer have reported that 85% of all deaths were due to causes other than prostate cancer after 10 years of follow-up and that after 15 years of follow-up, almost 90% of all deaths were due to causes other than prostate cancer [5, 30]. A US study reported that prostate cancer was the underlying cause of death in a third to one half of a cohort of older men with prostate cancer [31].

An underlying flawed assumption of the screening guidelines is that physicians can accurately predict an individual’s life expectancy, but, when considering a PSA test, average life expectancies are insufficient for informed decision making. Advancing age is often accompanied by comorbid conditions (such as heart disease or respiratory disease) that contribute to important variations in the median life expectancies within age groups. Therefore, estimates of life expectancy according to comorbidities might allow for better estimations of potential benefits and risks of screening older men rather than considering chronological age alone. For example, Walter and Covinsky [32] suggested using actuarial life expectancy estimates to approximate a patient’s risk of dying of a screen-detectable cancer, to aid in deciding if a patient is likely to benefit from screening for colorectal cancer. To apply a similar framework to screening for prostate cancer, consider a 70-year-old man with chronic obstructive pulmonary disease. Although the median life expectancy of a 70-year-old man is 12.4 years, this patient, because of his severe comorbidity, is probably in the lower quartile of life expectancy and is likely to live less than 7 years. Next, the risk of dying from prostate cancer for such a man, assuming no prior prostate cancer diagnosis (which would thus make him eligible to be screened with PSA testing), can be estimated by combining the prostate cancer incidence rate with the cause-specific prostate cancer survival rates over the 7-year period. In other words, one calculates the probability of the patient developing prostate cancer in the next year and dying from it within 7 years, plus the probability of the patient developing prostate cancer in 1–2 years and dying from it within 6 years, and so on [33]. This risk of such a patient dying of prostate cancer can be computed as about 0.3%. In contrast, a 75-year-old man in excellent health has a life expectancy of about 14 years. The prostate cancer mortality risk for this man (assuming no prior prostate cancer diagnosis) is similarly calculated at around 2%. This particular scenario argues against an age-specific cutoff for screening (e.g. at age 75) as there may be some older men who have the potential to benefit from screening. However, there are inherent uncertainties associated with this approach; although consideration of comorbidities may provide an improved estimate of an individual’s probability of dying from prostate cancer, a man may live substantially longer or shorter than his estimated life expectancy, resulting in an inaccurate calculation of his probability of dying from prostate cancer. Further, it may be impractical and time consuming for a physician to derive these estimates.

**Treatment of Prostate Cancer in the Older Man**

There is no cure for metastatic prostate cancer, which means there is a strong desire to find the cancer before it grows outside the prostate and becomes incurable. The PSA test can aid in the early detection of prostate cancer before it causes symptoms, and many men subsequently diagnosed with localized disease will be offered treatments designed to cure or control progression of their cancer. Treatment options include surgical removal of the prostate (prostatectomy), radiation therapy, hormone therapy and expectant management (‘watchful waiting’ or ‘active surveillance’). Unfortunately, in the absence of data from large randomized controlled trials, the most effective treatment option for older men remains uncertain. Indeed, a recent systematic review of the effectiveness of treatment for localized prostate cancer summarized the limitations of the literature and concluded that there is insufficient evidence to assess the benefits of various treatments [14]. One randomized controlled trial that did show a disease-specific survival benefit of radical
prostatectomy compared with watchful waiting reported that this finding was restricted to men aged less than 65 years [34].

Given that the average life expectancy of men in the USA is about 10 years at age 75 and that prostate cancer is frequently indolent, older men, particularly those with severe comorbidities, are unlikely to live long enough to benefit from treatment. Regardless of this, many men receive aggressive therapy for their diagnosis; a recent study reported that more than two thirds of men aged between 65 and 74 years and 40% of men aged 75 years or older diagnosed with low-risk prostate cancer received either radical prostatectomy or radiation therapy [15]. The lack of conclusive evidence for the effectiveness of treatment for localized disease, particularly in older men, presents a serious barrier to making well-informed decisions regarding clinical management of the disease. This further justifies the question of whether or not the cancer should even be screened for in the first place; however, it is plausible that some carefully selected men may benefit from PSA screening and treatment with curative intent later in life. For example, a recent study using a decision-analytic Markov model showed that men up to the age of 85 years who were healthy and had poorly differentiated cancer had improved survival with potentially curative treatment for their prostate cancer compared to those undergoing watchful waiting [35]. However, a major obstacle to selecting men for screening is the inability to differentiate between men who will have clinically nonsignificant disease and those whose cancer will eventually kill them.

**Targeted PSA Screening**

Deciding whom to screen and when is central to the issue of avoiding overdiagnosis and overtreatment of prostate cancer. While we can be reasonably confident that men with a life expectancy of less than 10 years are unlikely to benefit from screening, the value of screening only the healthy older for prostate cancer remains less clear. A recent post hoc analysis of the PLCO data suggests that screening men with no or minimal comorbidities may result in a mortality benefit when compared to screening men with at least one significant comorbidity [36]. Although this analysis included men aged 55–74, it provides some indication that there may be certain subgroups who might benefit from PSA screening. Indeed, Woloshin et al. [37] recently stratified individuals according to their smoking status to estimate the risk of dying from major causes of death, including prostate cancer. The risk charts indicate that current smokers and never smokers at age 65 have the same risk of dying from prostate cancer over the next 10 years, whereas smokers at age 75 are less likely to die from prostate cancer (and more likely to die from other causes, e.g. heart disease or chronic obstructive pulmonary disease) over the next 10 years than never smokers of the same age. Stratified and subgrouped analyses such as these may assist in the identification of subgroups of older patients who may benefit from PSA screening.

**Conclusion**

There are approximately 2 million prostate cancer survivors living in the USA. Current estimates of overdiagnosis suggest that many of these men may have been avoidably labeled as cancer patients. Consequently, a large proportion of them will also have undergone unnecessary treatment and may be living not only with the consequences of an unnecessary cancer diagnosis but with the resultant physical and psychological repercussions of aggressive therapy. The current modus operandi of opportunistic PSA screening in the older population is likely doing more harm than good. As the population continues to age and PSA testing remains the default option, we might expect a continued increase in overdiagnosis and overtreatment of prostate cancer in older populations. Further research to clarify the value of screening specific subpopulations may identify older men with the potential to benefit from PSA screening and medical intervention for their disease.

**References**


